I. Status of the Claims

Claims 1-8, 32, 41, 50, 60-62, 64, 73-81, 90 and 91 are pending. Claims 1-8 and 32 stand rejected. Claims 9-31, 33-40, 42-49, 52-59, 65-72 and 82-89 have previously been cancelled. Applicants gratefully acknowledge the rejoinder of groups I and III. *Office Action mailed May 8, 2006.* No new matter has been added.

II. Remarks

A. Rejections under 35 U.S.C. § 103(a)

The Examiner maintains the rejection of claims 1-8 and 32 as being allegedly unpatentable under 35 U.S.C. 103(a) over Richon et al. Proc. Natl. Acad. Sci. Vol. 95, pp. 3003-7 (1998) ("Richon") and WO0226696 to Watkins et al. ("Watkins").

In order to establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to the skilled artisan, to modify a reference or combine reference teachings. Second, there must be a reasonable expectation of success. The teaching or suggestion must be found in prior art or knowlege of one of ordinary skill in the art, not in the applicant's disclosure. Finally, the reference, or references when combined, much teach or suggest each and every claim limitation. M.P.E.P. 2143. Applicants respectfully submit that the Examiner has not met this burden.

The Examiner alleges that Richon discloses a compound that is a homolog of the presently claimed compounds, with a difference of only one $-CH_2-$ group. *Final Office Action* at p. 3. The Examiner contends that compound 7 of Richon reads on the claimed compound when R1 is phenyl, m is 0, and n is 5. Applicants note that m cannot be equal to 0 in the instant claims. Rather, m is equal to 1-10. Furthermore, the Board has held that a $-CH_2-$ homolog does not necessarily render a claim obvious, without more. *Ex parte Goonewardene*, 160 U.S.P.Q. 287 (Bs. Pat. App. 1968). Applicants again note that Examiner has pointed to no teaching, motivation or suggestion in Richon to modify compound 7. Therefore, the Examiner has not established a *prima facie* case of obviousness.

Regarding the rejection of the present claims over Watkins, the Examiner points to allegedly "similar" compounds, and contends "[c]learly the equivalency of the linkage to N or the Ch2 is equivalent." *Final Office Action* at p. 4. Applicants respectfully disagree. The Examiner has pointed to no teaching or suggestion that the amido linkages (-HNC(O)-) disclosed in Watkins are equivalent to the presently claimed urea linkages (-HNC(CO)NH-). The Examiner has further provided no motivation to modify the Watkins compounds to make the presently claimed invention.

B. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner maintains the rejection of claims 1-8 and 32 as being allegedly unpatentable under 35 U.S.C. § 112, first paragraph, for a lack of an enabling disclosure. *Final Office Action mailed on November 24, 2006*, p. 2. In the Final Office Action, the Examiner contends that the present rejection under § 112, first paragraph, is based on "make and use," and that Applicants have not enabled the use of these compounds because pharmaceutically uses are allegedly "unpredictable." *Final Office Action* at p. 3. Specifically, the Examiner contends that the specification "while being enabling for R1 to be a phenyl , does not reasonably provide enablement for any other cycloalkyl or any 3-10 membered heterocyclic group." *Office Action mailed May 8, 2006.*

In order to make a rejection for lack of enablement, the Examiner has the burden of establishing "a reasonable basis to question the enablement provided for the claimed invention." M.P.E.P. § 2164.04 (citing *In re* Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Furthermore, a specification "which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought **must be taken as being in compliance with the enablement requirement** . . . , unless there is a reason to doubt the objective truth of the statements contained therein . . . ." M.P.E.P. § 2164.04 (emphasis added). Applicants submit that the Examiner has failed to meet this burden.

As the Examiner noted in the previous Office Action, several factors are considered in determining whether any experimentation is undue, including: 1) the breadth of the claims; 2) the nature of the invention; 3) the state of the prior art; 4) the level of one of ordinary skill; 5) the level

of predictability in the art; 6) the amount of direction provided by the inventor; 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d at 737; M.P.E.P. 2164.01(a). Applicants further point out that 35 U.S.C. §112, first paragraph, requires that a patent must enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); M.P.E.P. § 2164.01. Nevertheless, "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." M.P.E.P. § 2164.01.

Regarding the first Wands factor, the Examiner contends that the claims encompass "very wide range of compounds." Applicants respectfully disagree that the present claims are unduly broad. Furthermore, as explained in more detail below, the breadth of the instant claims are fully enabled by the specification.

Regarding the second *Wands* factor, the nature of the invention, the Examiner merely states "the invention is a substituted compound that is useful to treat cancer." *Office Action mailed May 8, 2006*, at p. 3. The Examiner does not explain how this factor supports an enablement rejection.

Regarding the third *Wands* factor, the Examiner contends that the state of the prior art involves screening *in vitro* and *in vivo*, and that there is "no predictability and no established correlation between the different substitutions on a core that they would all behave in the exact same way." *Action mailed May 8, 2006*, at p. 3. Regarding the fifth *Wands* factor, the Examiner alleges that the pharmaceutical art is unpredictable, "requiring each embodiment to be individually assessed for physiological activity." *Office Action May 8,* 2006, at p. 3; *see also Final Office Action* at p. 3. Applicants respectfully note that neither the M.P.E.P. nor the case law requires, or even suggests, that each embodiment of a pharmaceutical claim must be individually assessed for physiological activity in order to establish enablement. The C.C.P.A. has explicitly stated that patent applicants are "**not required to disclose every species encompassed by their claims even in an unpredictable art.**" *In re Angstadt*, 537 F.2d 489, 502 (C.C.P.A. 1976) (emphasis added).

Indeed, *in vitro* models often are sufficient for establishing *in vivo* activity, even for method of treatment claims. *In re Brana*, 51 F.3d 1560, 1565 (Fed. Cir. 1995); *see also* M.P.E.P. 2164.02.

The Federal Circuit in *Brana* held that *in vitro* tumor models were sufficiently enabling for the treatment of cancer. Similarly, the *in vitro* data of HDAC inhibition, cytotoxicity in SQ-20B cells, and radiation clonigenic survival rates assays described in the instant specification sufficiently enable the use of the presently claimed compounds. *Specification* at Tables 3 and 4. As explained in the specification, HDAC inhibitors are known in the art as sensitizing agents in radiation therapy, *Specification* at p. 3. The data presented in Tables 3 and 4 confirm this fact. Accordingly, the presently claimed compounds would be expected to be useful in inhibition of HDAC activity, increasing sensitovity of cancer cells to the cytotoxic effects of radiation and the treatment of cancer. Thus, factors 3 and 5 also support enablement of the instant claims.

With respect to the fourth *Wands* factor, the ordinary artisan is highly skilled, as the Examiner previously noted. *Office Action mailed May 8, 2006*, at p. 3.

Regarding the sixth *Wands* factor, the Examiner states that the inventors provides "little direction in the instant specification," and further contends that that all of the compounds shown in Tables 3 and 4 of the instant application have either a phenyl or adamantyl, and do not cover the scope of the claimed genus of aryl, cycloalkyl and heterocyclyl. *Final Office Action* at p. 3. To the contrary, examples 1-8, depicted in Tables 3 and 4, in fact include examples of both aryl and substituted aryl (e.g., dimethylaminophenyl), as well as cycloalkyl (e.g., adamantyl). In Applicants' previous response, Applicants pointed to synthetic scheme I (Specification p. 31), demonstrating that the preparation of such compounds has indeed been enabled. *Response mailed September 8, 2006*. This evidence establishes that those skilled in the art would readily know make the claimed compounds based on the guidance provided in the instant application. The Examiner has not denied that Scheme I, in addition to examples 1-8, sufficiently enable the skilled artisan to at least make the presently claimed compounds.

Nevertheless, the Examiner contends that the present rejection under § 112, first paragraph, is based on "make and use," and that Applicants allegedly have not enabled the use of these compounds because pharmaceutically uses are allegedly "unpredictable." *Final Office Action* at p. 3. As discussed above, Applicants data establishes HDAC inhibition, cytotoxicity and increased

radiation sensitivity in compounds having aryl, substituted aryl and cycloalkyl groups, as well as compounds having varied values for m and n. *Specification* at Tables 3 and 4.

Regarding the seventh and eighth Wands factors, the Examiner contends that the specification has "no working examples nor any invitro or invivo data that they do have any activity," and therefore, "the amount of experimentation is very high and burdensome." *Office Action mailed May 8, 2006*, at p. 4. As explained in detail above, the specification provides many working examples, including *in vitro* data demonstrating HDAC inhibition, cytotoxicity in SQ-20B cells, and radiation clonigenic survival data for compounds encompassed by the instant claims. *Specification* at Tables 3 and 4. Thus, Applicants have amply demonstrated *in vitro* activity for the present compounds. Furthermore, as dicussed above, *in vivo* data is not required to establish enablement for *in vivo* treatment claims. *See In re Brana*, 51 F.3d. at 1565-6. Moreover, "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." M.P.E.P. § 2164.01; *In re Brana*, 51 F.3d. at 1565-6.

Applicants also respectfully point out that the Examiner's analogy to caffeine and theophylline is inaccurate. *Office Action mailed May 8, 2006*, at p. 3. In fact, caffeine and theophylline have both similar structure and activity. (See Snyder et al.; Chapman et al; and Wikipedia; all attached). The attached references demonstrate that the xanthine class of compounds, as a whole, possess similar biological activity. For example, Snyder et al. demonstrates that caffeine and theophylline have several biological activities in common, such as the reversal of L-PIA evoked depression and stimulation of locomotor activity (see Abstract and Fig. 1), and hypothesizes that the entire class of xanthines exhibits behavioral stimulant effects due to the blockade of central adenosine receptors (Abstract). Chapman et al. notes that caffeine "shares a variety of its pharmacological properties with the other naturally occurring methylxanthines, theophylline and theobromine. (Chapman at 616, ll. 2-17.) According to Wikipedia, theophylline "bears structural and pharmacological similarity to caffeine." (Wikipedia, Theophylline, at p. 1). Thus, the theophylline/caffeine comparison demonstrates that, contrary to the Examiner's contention, those skilled in the art would expect the claimed genus of compounds to possess similar activity.

For at least the reasons set forth above, Applicants submit that the instant claims are fully enabled in accordance with 35 U.S.C. § 112, first paragraph.

III. Conclusion

In light of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone interview would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, GUX-012.01.**

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Respectfully submitted,

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